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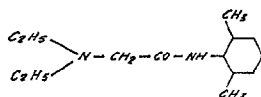
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COMPLETE SPECIFICATION

A Hydrate of Lignocaine Hydrochloride and process for making it

We, ARTHUR POOLE, a British Subject, of 11 Nutfield Gardens, Goodmayes, Essex, and CHARLES LESLIE MEFEDITH BROWN, a British Subject, of 23 Elmstead Close, Ewell, Surrey, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the local anæsthetic substance known as "lignocaine," which is N-diethylaminoacetyl-2:6-dimethyl-anilide and has the formula:



When the lignocaine is required for use, it has been customary for the free base to be dissolved in a calculated quantity of hydrochloric acid to produce an aqueous solution of lignocaine hydrochloride. The concentration and pH value of this solution have usually had to be carefully adjusted. It would, therefore, be a distinct advantage if lignocaine hydrochloride could be made available in a solid form which the anæsthetist could use for preparing an aqueous solution by simple dissolution in water.

Attempts made in this direction have not been encouraging. Thus, the hydrochloride obtained by concentrating an aqueous solution thereof takes the form of an intractable, lumpy mass of doubtful composition. The hydrochloride obtained as a solid precipitate by passing hydrogen chloride gas into a solution of the free base in an organic solvent, in which the hydrochloride is insoluble or sparingly soluble, is so hygroscopic that it must be packed in air-tight containers for storage or transport.

The present invention is based on the observation that lignocaine hydrochloride can be obtained in the form of a monohydrate which is a stable and non-hygroscopic substance that can be produced in the form of discrete particles.

Accordingly, the invention provides, as a new substance, lignocaine hydrochloride monohydrate in the form of discrete particles.

The invention also provides a process for the manufacture of lignocaine hydrochloride monohydrate, wherein lignocaine hydrochloride is combined with the quantity of water necessary to form the monohydrate and the latter is converted into discrete particles.

The process may be carried out in various ways. In one form of the process discrete particles of the monohydrate are precipitated from a solution of the hydrochloride in a solvent medium comprising a limited proportion of water at least sufficient to form the monohydrate and in the presence of a water-miscible organic liquid in which the monohydrate is insoluble or sparingly soluble.

This form of the process is advantageously carried out by precipitating the monohydrate from an aqueous solution of the lignocaine hydrochloride by mixing the solution with the water-miscible organic liquid. An alternative method of precipitating discrete particles of the monohydrate from solution in the presence of the water-miscible organic liquid is to crystallise the monohydrate from a solution of the hydrochloride in a solvent medium consisting of a mixture of water with the water-miscible liquid. Crystallisation may be brought about, for example, by cooling a solution of the hydrochloride in the solvent mixture. Both of these methods depend on the presence of an adequate proportion of the water-miscible liquid in relation to water to cause the monohydrate to separate out of solution.

Examples of suitable water-miscible organic liquids in which the monohydrate is insoluble or sparingly soluble are acetone, methyl ethyl ketone and dioxane.

It is to be understood that "a limited proportion of water" includes as the lower limit the proportion required to form the monohydrate.

hydrate, and as the upper limit a proportion of water in relation to the proportion of hydrochloride not exceeding that beyond which an unduly large percentage of the hydrochloride remains in solution. The upper limit is, therefore, largely dependent on economic considerations. In order to obtain a satisfactory yield of the solid monohydrate, it will generally be of advantage not greatly to exceed the quantity of water theoretically required to form the monohydrate. Thus, for example, in precipitating the monohydrate from an aqueous solution of the hydrochloride by the addition of acetone, the proportion of water in excess of the theoretical amount may be up to about 5 molecular proportions per molecular proportion of the hydrochloride, or even up to about 20 molecular proportions if the temperature is sufficiently low, say, about 3°C. There is also an optimum proportion of acetone giving a maximum yield of precipitate, above and below which the yield is lower.

An aqueous solution of the hydrochloride, from which the monohydrate is to be precipitated as described above, may conveniently be prepared by taking up the free base in water with the aid of hydrochloric acid, and it is of advantage to use a proportion of the acid slightly less than that required to convert the whole of the base into the hydrochloride. If the solution so obtained contains an excess of water (i.e. a quantity of water in excess of that required to form the monohydrate) greater than that desired, the excess may be decreased by removing water from the solution by evaporation or by azeotropic distillation with a suitable organic liquid, such as benzene.

In order to prepare a solution of the monohydrate in a mixture of water with the water-miscible organic liquid, from which solution the monohydrate is to be crystallised as described above, gaseous hydrogen chloride may be passed into a mixture of the free base with the water and water-miscible liquid so as to take up the base into solution as the hydrochloride.

In the methods mentioned above, it is desirable for economic reasons to recover the dissolved base and the water-miscible solvent from the mother liquors resulting from the precipitation or crystallisation of the hydrochloride monohydrate. This may be done by removal of solvent, for example, acetone, by a process of distillation followed by recovery of the lignocaine from the residual hydrochloride syrup. This may be carried out by treatment with ammonium hydroxide solution. Alternatively the residue may be used in a further operation for the production of the hydrochloride monohydrate.

A further form of the process of the invention consists in converting lignocaine hydrochloride, which is anhydrous or contains less than one molecular proportion of water, into

the monohydrate by bringing it into contact with water vapour until the hydrochloride has taken up the amount of water necessary to form the monohydrate, and the latter is brought into the form of discrete particles by dissolving it in a solvent and crystallising it from the solution.

In order to form the monohydrate in this manner the hydrochloride may be treated with a gas containing water vapour, such as humid air, and care taken that the gas gains adequate access to the whole of the hydrochloride. For the latter purpose it may be necessary to disintegrate sticky and lumpy material initially formed or to agitate the hydrochloride during the hydration to prevent the formation of such material. It is of advantage to use air at normal atmospheric humidities, because then the absorption of water does not proceed beyond the monohydrate stage, so that no special measures, such as stopping the hydration when the appropriate amount of water has been taken up, are necessary to prevent excessive hydration.

The following Examples illustrate the invention:

EXAMPLE 1.

138 grams of lignocaine (melting at 67—68°C.) were dissolved in 54 cc of concentrated hydrochloric acid of about 33 per cent. strength by weight, and 660 cc of acetone were added. The mixture was stirred at 25—30°C. for 1½ hours in order to complete the precipitation of lignocaine hydrochloride monohydrate, which separated out in a granular crystalline form. The monohydrate was then filtered off. There were obtained 110 grams of the monohydrate melting at 77—78°C. The mother liquor was worked up to recover acetone and lignocaine.

If 59.5 cc of hydrochloric acid of 30 per cent. strength by weight are used, instead of the quantity and strength of hydrochloric acid mentioned above, approximately the same quantity of the monohydrate is obtained by carrying out the precipitation at 17°C; and approximately the same yield is obtained at 10°C. when 71.3 cc of hydrochloric acid of 25 per cent strength by weight are used.

If, in the procedure described in the first paragraph of this Example, twice the volume of acetone (1320 cc) is used approximately the same yield of monohydrate is obtained by carrying out the precipitation at 17°C. and with three times the volume of acetone (1980 cc) the same is true at 15°C.

EXAMPLE 2.

A solution of 20 grams of lignocaine in the quantity of 2N-hydrochloric acid necessary to form the hydrochloride was dehydrated by subjecting the solution to azeotropic distillation with benzene until no more water passed over. The resulting lignocaine hydrochloride was dissolved at about 60°C. in a mixture of 70 cc of methyl ethyl ketone and 1.2 cc of

water. The latter quantity of water together with the small amount already present in the hydrochloride amounted to slightly more than one molecular proportion per molecular proportion of the hydrochloride (calculated as anhydrous). The hot solution was allowed to cool to room temperature overnight, and the crystalline monohydrate so formed was filtered off. There were obtained 22.5 grams of lignocaine hydrochloride monohydrate melting at 77—78°C. The mother liquor was worked up to recover methyl ethyl ketone and lignocaine.

If the total amount of water is increased to 3 molecular proportions per molecular proportion of the hydrochloride by adding 4.5 cc, instead of 1.2 cc, of water, the same yield of the monohydrate can be obtained by cooling the hot solution to a lower temperature of the order of 3°C.

EXAMPLE 3.

5 grams of lignocaine hydrochloride, which had been dehydrated as described in Example 2, were exposed at 20°C. to air having a relative humidity of 50% at that temperature. The material became sticky and hardened to a lumpy mass after 2 hours. The mass was ground to a fine powder, and then exposed to air under the same conditions for a further 24 hours, during which it did not become lumpy. The hydrated material was then dissolved in 18 cc of methyl ethyl ketone at 60°C, and the solution was cooled to room temperature. 4 grams of lignocaine hydrochloride monohydrate crystallised out. Owing to the tendency for large crystals to form, the solution may be stirred during cooling if crystals of smaller size are desired.

What we claim is:—

1. Lignocaine hydrochloride monohydrate in the form of discrete particles.

2. A process for the manufacture of lignocaine hydrochloride monohydrate, wherein lignocaine hydrochloride is combined with the quantity of water necessary to form the mono-

hydrate and the latter is converted into discrete particles.

3. A process as claimed in claim 2, wherein discrete particles of lignocaine hydrochloride monohydrate are precipitated from a solution of lignocaine hydrochloride in a solvent medium comprising a limited proportion of water at least sufficient to form the monohydrate and in the presence of a water-miscible organic liquid in which the monohydrate is insoluble or sparingly soluble.

4. A process as claimed in claim 3, wherein the monohydrate is precipitated from an aqueous solution of lignocaine hydrochloride by mixing the solution with the water-miscible organic liquid.

5. A process as claimed in claim 3, wherein the monohydrate is crystallised from a solution of the hydrochloride in a mixture of water and the water-miscible liquid.

6. A process as claimed in claim 5, wherein the crystallisation is brought about by cooling the solution of the hydrochloride.

7. A process as claimed in claim 2, wherein lignocaine hydrochloride is converted into the monohydrate by bringing it into contact with water vapour until the hydrochloride has taken up the amount of water necessary to form the monohydrate, and the latter is brought into the form of discrete particles by dissolving it in a solvent and crystallising it from the solution.

8. A process for the manufacture of lignocaine hydrochloride monohydrate, conducted substantially as described in Example 1, 2 or 3 herein.

9. Lignocaine hydrochloride monohydrate whenever made by the process claimed in any one of claims 2—8.

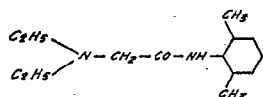
ABEL & IMRAY,
Agents for the Applicants,
Quality House, Quality Court,
Chancery Lane, London, W.C.2.

PROVISIONAL SPECIFICATION

A Hydrate of Lignocaine Hydrochloride and process for making it

We, ARTHUR POOLE, a British Subject, of 11 Nutfield Gardens, Goodmayes, Essex, and CHARLES LESLIE MEREDITH BROWN, a British Subject, of 23 Elmstead Close, Ewell, Surrey, do hereby declare this invention to be described in the following statement:—

This invention relates to the local anæsthetic substance known as "lignocaine," which is N-diethylaminoacetyl-2:6-dimethyl-anilide and has the formula:



When the lignocaine is required for use, it has been customary for the free base to be dissolved in a calculated quantity of hydrochloric acid to produce an aqueous solution the concentration and pH value of which usually have to be adjusted.

It would, however, be desirable that lignocaine hydrochloride be available in a stable, easily handled solid form which the anæsthetist could prepare for use by simple dissolution in water.

When attempts are made to isolate the hydrochloride in solid form from aqueous solution by concentrating the solution, an intractable lumpy mass of doubtful composition is obtained.

By passing hydrogen chloride gas into a solution of lignocaine in the form of the free base in an organic solvent in which the hydrochloride is insoluble or sparingly soluble, the hydrochloride can be precipitated in solid form. However, the hydrochloride so obtained is extremely hygroscopic, so that it must be packed in air-tight containers for storage and transport, and it is difficult to handle in making it up into preparations suitable for administration.

The present invention is based on the observation that lignocaine hydrochloride can be obtained in the form of discrete particles of a monohydrate which is non-hygroscopic.

Accordingly, the invention provides, as a new substance, lignocaine hydrochloride monohydrate. Samples of this substance have been made having a melting point within the range of 77° C. to 80° C.

The invention also provides a process for the manufacture of the said monohydrate, wherein lignocaine hydrochloride is caused to combine with a quantity of water such that the final product contains one molecular proportion of water per molecular proportion of the hydrochloride.

The process may be carried out in various ways. In one form of the process the monohydrate is caused to separate out in solid form from a solution of the hydrochloride in a solvent medium comprising a limited proportion of water at least sufficient to form the monohydrate, and in the presence of a water-miscible organic liquid in which the monohydrate is insoluble or sparingly soluble.

This form of the process is advantageously carried out by adding an aqueous solution of the hydrochloride of suitable concentration to the water-miscible organic liquid under such conditions as to cause the precipitation of the monohydrate. An alternative method of causing the monohydrate to separate out from solution in the presence of the water-miscible organic liquid is to cause the monohydrate to crystallise from a solution of the hydrochloride in a solvent medium consisting of a mixture of water with the water-miscible liquid. Crystallisation may be brought about by a method in itself known, for example, by cooling a solution of the hydrochloride in the solvent mixture. Both of these methods depend on the presence of an adequate proportion of the water-miscible liquid in relation to water to cause the monohydrate to separate out of solution.

Examples of suitable water-miscible organic liquids in which the monohydrate is insoluble or sparingly soluble are water-miscible ketones, for example, acetone or methyl ethyl ketone, and a further example is dioxane.

It is to be understood that "a limited proportion of water" includes as the lower limit the proportion required to form the monohydrate, and as the upper limit a proportion

of water in relation to the proportion of hydrochloride not exceeding that beyond which an undesirably large percentage of the hydrochloride remains in solution. The upper limit is, therefore, largely dependent on economic considerations. In order to obtain a satisfactory yield of the solid monohydrate, it will generally be of advantage not greatly to exceed the quantity of water theoretically required to form the monohydrate. Thus, for example, in precipitating the monohydrate from an aqueous solution of the hydrochloride by the addition of acetone, the proportion of water in excess of the theoretical amount may be up to about 5 molecular proportions per molecular proportion of the hydrochloride, or even up to about 20 molecular proportions if the temperature is sufficiently low, say, about 3°C. There is also an optimum proportion of acetone giving a maximum yield of precipitate, above and below which the yield is lower.

An aqueous solution of the hydrochloride, from which the monohydrate is to be precipitated as described above, may conveniently be prepared by taking up the free base in water with the aid of hydrochloric acid, and it is of advantage to use a proportion of the acid slightly less than that required to convert the whole of the base into the hydrochloride. If the solution so obtained contains an excess of water (i.e. the quantity of water in excess of that required to form the monohydrate) greater than that desired, the excess may be decreased by removing water from the solution by evaporation or by azeotropic distillation with a suitable organic liquid, such as benzene.

In order to prepare a solution of the monohydrate in a mixture of water with the water-miscible organic liquid, from which solution the monohydrate is to be crystallised as described above, gaseous hydrogen chloride may be passed into a mixture of the free base with the water and water-miscible liquid so as to take up the base into solution as the hydrochloride.

In the methods mentioned above, it is desirable for economic reasons to recover the dissolved base and the water-miscible solvent from the mother liquors of precipitation or crystallisation of the hydrochloride monohydrate. This may be done by removal of solvent, for example acetone, by a process of distillation followed by recovery of the lignocaine from the residual hydrochloride syrup. This may be carried out by treatment with ammonium hydroxide solution. Alternatively the residue may be used in a further operation for the production of the hydrochloride hydrate.

A further form of the process of the invention consists in causing lignocaine hydrochloride, which is anhydrous or contains less than the quantity corresponding to one molecular proportion of water, to combine with the

quantity of water necessary to form the monohydrate. For this purpose the hydrochloride may be brought into contact with water vapour until the hydrochloride has taken up the necessary amount of water. For example, a gas containing water vapour, such as humid air, may be passed over the hydrochloride while the latter is agitated to ensure adequate contact with the humid gas, which is advantageously used near its saturation point.

The following Examples illustrate the invention:

EXAMPLE 1.

138 grams of lignocaine (melting at 67—68°C.) were dissolved in 54 cc of concentrated hydrochloric acid of about 33 per cent. strength by weight, and 660 cc of acetone were added. The mixture was stirred at 25—30°C. for 1½ hours in order to complete the precipitation of lignocaine hydrochloride monohydrate, which separated out in a granular crystalline form. The monohydrate was then filtered off. There were obtained 110 grams of the monohydrate melting at 77—78°C.

The mother liquor was worked up to recover acetone and lignocaine.

EXAMPLE 2.

A solution of 20 grams of lignocaine in the quantity of 2N-hydrochloric acid necessary to form the hydrochloride was dehydrated by subjecting the solution to azeotropic distillation with benzene until no more water passed over. The resulting lignocaine hydrochloride was dissolved at about 60°C. in a mixture of 70 cc of methyl ethyl ketone and 1.2 cc of water. The latter quantity of water together with the small amount already present in the hydrochloride amounted to slightly more than one molecular proportion per molecular proportion of the hydrochloride (calculated as anhydrous). The hot solution was allowed to cool to room temperature overnight, and the crystalline monohydrate so formed was filtered off. There were obtained 22.5 grams of lignocaine hydrochloride monohydrate melting at 77—78°C.

The mother liquor was worked up to recover methyl ethyl ketone and lignocaine.

ABEL & IMRAY,
Agents for the Applicants,
Quality House, Quality Court,
Chancery Lane, London, W.C.2.